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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	**Lichtenberger, Lenard M.**	§	EXAMINER: **JIANG**
SERIAL NO:	**09/827,493**	§	GROUP ART UNIT: **1617**
FILED:	**04/06/01**	§	DOCKET: **96606/15UTL**
		§	
FOR:	**Unique Composition of Zwitterionic Phospholipids and Bisphosphonates with Reduced Toxicity and Enhanced Bioavailability**	§	

EV 123 140 689 US Number	**CERTIFICATE OF MAIL BY EXPRESS MAIL**	February 13, 2003 Date of Deposit

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Assistant Commissioner of Patent
Washington, D.C. 20231

Robert W. Strozier — February 13, 2003 Date of Signature

ARGUMENTS RELATING TO OBVIOUSNESS

Dear Examiner:

This arguments are designed to address the Examiner's contention that claims **1-32** of this application are obvious and, therefore, unpatentable over Daifotis, et al. (WO 9904773) in view of Lichtenberger et al. under 35 U.S.C. §103(a).

The Examiner contends as follows:

> Applicant's remarks filed on June 5, 2002 in Paper No.10 with respect to this rejection of claims 1-32 made under 35 U.S.C. 103(a), of record stated in the Office Action dated February 12, 2002 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for the following reasons.
>
> Applicant arguments that there is no motivation to combine because there is no reasonable expectation that their combination would be successful are not found to be persuasive. As Applicant admits, Daifotis et al. clearly teaches that bisphosphonates can cause adverse GI effects when ingested. Daifotis et al. also disclose that their invention relates to methods for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the occurrence of or potential for adverse GI effects (see page 1 lines 11-13). Thus, the teachings of Daifotis et al. are seen to provide the motivation to make the present invention in reducing GI toxicity.
>
> Moreover, zwitterionic phospholipids (within the instant claims) are known to be capable of reducing GI irritating (adverse) effects and is therefore

useful in combining with NSAID drugs in pharmaceutical compositions since NSAID drugs may cause GI adverse effects, e.g., inducing GI ulcers and bleeding, according to Lichtenberger et al. As discussed in the previous Office Action, one of ordinary skill in the art, therefore, w ould have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonate in a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate with reasonable expectation for success, absent evidence to the contrary.

Additionally, the teachings of Hovancik et al. (5,869,471, PTO-892) that the combination of NSAIDs and bisphosphonates is useful in improving the therapeutic effect for treating arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7), further supports the examiner's position, since that the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders. Thus, one of ordinary skill in the art would reasonably expect that the combination of bisphosphonates and zwitterionic phospholipids would be successful in treating bone disorders.

Applicant's arguments regarding that "the motivation to combine these to references is derived exclusively from hindsight" have been considered but are not found persuasive. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

Therefore, as discussed above, motivation to combine the teachings of the prior art to make the present invention is seen and no improper hindsight is seen. The claimed invention is clearly obvious in view of the prior art.

The record contains no clear and convincing evidence of nonobviousness or unexpected results for the combination herein over the prior art. In this regard, it is noted that the specification provides no side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant has submitted a Rule 132 Declaration in support of Applicant's contention that the invention is not obvious over Daifotis, et al. (WO 9904773) in view of Lichtenberger et al. Applicant states in his Declaration that research performed at his request demonstrate

that bisphosphonates disrupt the packing efficiency and stability of PC monolayer, a model of the lining of the GI tract. Applicant also states that the out come of the combination of PCs and bisphosphonates could have shown no reduction in bisphosphonate GI toxicity or if mixed liposomes and/or micelles had formed, then the PCs could well have increased the concentration of bisphosphonates at the mucosal lining of the GI tract increasing bisphosphonate GI toxicity.

Applicant still contends that there is nothing in the cited references that suggest to combine PCs with pharmaceuticals very different from NSAIDS and that possess a very similar structure to the PC. There simply is not disclosure, teaching or suggestion that PC can protect the GI tract from any agent that causes GI toxicity. In fact, because liposomes are known structures for transporting pharmaceuticals such as RNA, DNA, proteases, etc. to cell membranes and other hydrophobic membranes, one skilled in the art could have concluded that the combination the PCs and bisphosphonates would enhance bisphosphonate GI toxicity.

A major problem with pharmaceuticals, and chemicals in general, is that the effects of combinations cannot generally predicted a prior, especially, when the combination that are being compared to the new composition includes compounds that have little in common - NSAIDs versus bisphosphonates. It is well known that even minor changes to a composition or formulation can result in unpredictable changes in activity, mode of activity, efficacy, bio-availability, *etc.*; sometimes resulting in extremely dangerous consequences.

Interestingly, the Examiner cites Hovancik et al. arguing for the combinability of these two references. However, the Hovancik et al. combination is one such situation, where the combination of two pharmaceuticals generates an unexpected result. The combination of these two medications, NSAIDs and Bisphosphonates, nearly doubles the occurrence of GI ulcers in patients given the drug combination vs. patients given each drug individually. See attached a rticle a bstract: G raham D Y a nd M alaty H M, " Alendronate a nd n aproxen a re synertistic for development of gastric ulcers," Arch Intern Med, **161**; 1862 (2001). Thus, these two drugs synergize GI toxic effects, showing that there is simply no known procedure for determining *a priori* how two pharmaceutical c ompounds will behave in the body.

Therefore, Hovancik et al. merely show how unpredictable combinations of pharmaceuticals are and how such combinations often give rise to unexpected results – bad results in this case.

Applicant, moreover, believes that one of ordinary skill in the art would not compare an NSAID to a bisphosphonate. These two class of compounds are just too different. NSAIDs do not contain phosphate groups, while bisphosphonates not only contain one, but two phosphate groups. Moreover, because PCs and bisphosphonates are structurally similar both being zwitterions at biologic pHs, because bisphosphonates have a greater head charge density (double) and because bisphosphonates have lower molecular weight compounds than PCs, one of ordinary skill in the art simply has insufficient information to determine how a combination of these two compounds would behave in the body.

Therefore, based on the chemical facts stated above and the fact that combined administration of NSAIDs and bisphosphonates result in a doubling of GI toxic effect over an accumulative effect, an ordinary artisan could come to the conclusion that phospholipids would be an ineffective means for reducing GI toxicity effects of orally administered bisphosphonates.

Applicant still believes the motivation to combine these two references is derived exclusively from hindsight. Although the Examiner recognized that the invention itself cannot be used to construct an obvious rejection, the Examiner contends that "so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper." In this case, however, the knowledge of one skilled in the art does not lead to this invention. As stated above, the information as a whole would suggest on unknown outcome at best.

Applicant continues to believe that Daifotis et al. actually teaches away from any motivation to an ordinary artisan to reduce GI toxicity effects of bisphosphonates because Daifotis et al. unequivocally teaches that the problem of GI toxicity of bisphosphonates has been solved and its solution is simply based on using a "continuous schedule" having a selected dosing interval. Thus, to an ordinary artisan, there is no reason to solve a non-

existent problem – Daifotis et al. solved the problem. The Examiner even admits that the Daifotis et al. method minimizes the adverse GI effects induced by bisphosphonate. So why, then would an ordinary artisan look to Daifotis et al. to solve a solved problem, one that Daifotis et al. teaches they solution. Where is the motivation? It simply is absent.

In summary, the combination of the references does not render this invention obvious. The chemistry and pharmacology simply do not support such a conclusion, without the results of this invention, an improper use of highsight. In fact, the chemistry and pharmacology can be used to support the exact opposite conclusion – phospholipids would have either no affect or would enhance the adverse affect by transporting the bisphosphonates to the lining of the GI tract. Applicant, therefore, respectfully requests withdrawal of this 103(a) rejection and allowance of the case.

If it would be of assistance in resolving any issues in this application, the Examiner is kindly invited to contact applicant's attorney Robert W. Strozier at 713.977.7000

Date: **February 13, 2003**

Respectfully submitted,

Robert W. Strozier
Reg. No. 34,024